

REQUEST FOR RECONSIDERATION

Applicants thank Examiner Keys for the helpful and courteous discussion of November 5, 2004. During the discussion, Applicants' U.S. representative presented arguments that a process that requires the reaction of a perfluoroalkylolefin with an alcohol cannot render obvious a process which requires the reaction of a perfluoroolefin with an alcohol. Applicants' U.S. representative pointed out that both the starting materials and the products of the invention process are chemically different materials from the starting materials and products of the processes described in the prior art relied upon by the Office.

Applicants have disclosed a process wherein a fluoroalkanol may be produced in high selectivity. Example 2 of the present application describes the preparation of 2,2,3,3-tetrafluoropropanol from methanol and tetrafluoroethylene. The process disclosed in Example 2 proceeds by continuously adding tetrafluoroethylene and a radical initiator (di-tert-butyl peroxide) to methanol. The target compound 2,2,3,3-tetrafluoropropanol is formed with a selectivity of 95% (page 12, lines 20-21).

The Office has asserted that the presently claimed process is obvious in view of a combination of patents to Joyce (U.S. 2,559,628), Satokawa (U.S. 4,346,250) and Knaup (U.S. 5,227,540). Applicants traverse the rejection on grounds including (1) the Office's failure to demonstrate that a perfluoroolefin and a perfluoroalkyl ethylene may be expected to exhibit the same type of reactivity and a reaction carried out on one would be expected proceed in the same way for the other, and (2) the significantly superior selectivity observed in the claimed process.

The Office admits that Joyce does not disclose the continuous addition of a perfluoroolefin and a radical initiator to form a fluoroalkanol but instead discloses a batch process (see page 4 of the Office Action of October 7, 2004). The Office applies Knaup for its disclosure of a process wherein a fluoroalkylethylene of formula $R_f-CH=CH_2$ is added to

an alkanol to form a fluoroalcohol of formula $R_f-CH_2-CH_2-CH(R)-OH$ (this may be compared with the claimed invention where, for example, a perfluoroolefin of formula $R_f-CF=CF_2$ may be reacted with an alkanol to form a fluoroalcohol of formula $R_f-CFH-CF_2-CH_2-OH$). The Office asserts on the last three lines of page 4 of the Office Action of October 7, 2004 that “the reaction conditions and concentrations of the process of Knaup overlap with those of the instant claims.”

Applicants traverse the Office’s assertion that Knaup teaches reaction conditions that overlap with the conditions required in the present claims. The present claims require the reaction of a perfluoroolefin with an alkanol. A perfluoroolefin is a compound of formula $CF_2=CFR_f$. In contrast, Knaup discloses perfluoroalkyl ethylenes of formula $CH_2=CH-R_f$. The difference between the perfluoroalkylethylene of Knaup and the perfluoroolefin of the present application are immediately evident. The perfluoroalkylethylene of Knaup does not have a fluorine atom (e.g., an F atom) bonded to a carbon atom of an ethylenically unsaturated unit.

Applicants submit that it is readily evident to those of ordinary skill in the art that a perfluoroolefin and a perfluoroalkylethylene are different compounds with different reactivity. As support Applicants submit herewith pages 70-73 of “*Compound of Fluorine*” published on February 1, 1979. The attached pages in the Japanese language demonstrate the electron withdrawing effect of the fluorine atom on the reactivity of the olefinic material.

It is not possible for Knaup to disclose the reaction conditions of the presently claimed process as evidenced by the fact that Knaup teaches a different olefinic material and forms a different product. The difference in starting materials between the Knaup patent and the present claims has a material impact on the process as evidenced by the products formed by the claimed process in comparison to the products formed in the prior art process. The fluoroalkanol formed in the claimed process has formula $H(CFR^3CF_2)_n-CR^1R^2-OH$ where R^1

and R^2 may be a hydrogen atom or a C_{1-3} alkyl group. In the fluoroalkanol formed in the process of the present invention the β -carbon atom is substituted with at least two fluorine atoms.

In contrast, the product formed by the Knaup process is of formula $R_1-CH_2-CH_2-C(R)H-OH$. The closest carbon atom that is substituted with a fluorine atom in the product formed by the Knaup process is at a δ position. The fluorine substitution occurs at the fourth carbon position in the product of Knaup whereas fluorine substitution occurs at the second carbon position in the product produced by the claimed process.

Applicants submit that it is readily recognized by those of ordinary skill in the art that the presence of the two additional $-CH_2-$ units in the product of the prior art reaction will have a material effect on the acidity of the prior art product. This difference in acidity may have a material effect on the reaction conditions occurring inside a reactor because the acidity of the reaction mixture can affect the formation of emulsions and the operation of phase transfer within an emulsion. It is known to those of ordinary skill in the art that the effect of fluorine substitution on acidity of organic compounds is caused at least in part by an inductive effect of the highly electronegative fluorine atom. A description of the inductive effect is included in the attached pages 153-155 of F.G. Bordwell, "*Organic Chemistry*," The MacMillan Co., New York (1963). This effect is further demonstrated by pages 521-523 of volume 11 of "*Kirk-Othmer Encyclopedia of Chemical Technology*," 4th ed., Wiley-Interscience, New York (1994) where the relative acidities of mono-, di- and tri-fluoro substituted ethanol is described (copy attached).

The Office has provided no evidence that those of ordinary skill in the art would expect a perfluoroalkylethylene to react in the same manner as a perfluoroolefin. Applicants submit that those of ordinary skill in the art would not be led to believe that a

perfluoroalkylethylene will react in the same manner as a perfluoroolefin when reacted with an alkanol.

The Office has provided no support that there is an art recognized equivalence between processes of reacting perfluoroolefins with alcohols and processes of reacting perfluoroalkylethylenes with an alkanol.

It appears that the Office is asserting that because Knaup teaches a process of continuously adding a radical initiator and a perfluoroalkylefin to an alcohol, the claimed method of adding a perfluoroolefin and a radical initiator to an alcohol must be obvious. However, the Office has not however provided any support for the assertion that one of ordinary skill in the art would recognize that a perfluoroolefin and a perfluoroalkylethylene are obvious in view one another.

While it is known that compounds having a close structural similarity such as homologues and isomers may be obvious in view of one another, Applicants submit that perfluoroolefins and perfluoroalkylethylenes are not homologues or isomers of one another (MPEP § 2144). Perfluoroolefins necessarily have a greater number of fluorine atoms than any corresponding hydrofluoroolefin. Further, the fluorine atoms in a perfluoroolefin are present at the carbon-carbon double bond. There is no fluorine present in the carbon-carbon unsaturation of a perfluoroalkylethylene.

As support that a perfluoroalkylethylene and a perfluoroolefin may have different reactivities Applicants attached herewith pages 499-503 of volume 11 of "*Kirk-Othmer Encyclopedia of Chemical Technology*", 4th ed., Wiley-Interscience, New York (1994). Tables 1 and 2 on pages 501 and 502, respectively, provide a comparison of the properties of aliphatic perfluorocarbons and hydrofluorocarbons. As stated on page 499 lines 2 and 3 from the bottom "[a]liphatic PFCs [e.g., perfluorocarbons] have an unusual combination of properties relative to their hydrocarbon counterparts." Applicants submit that it is readily

recognized by those of ordinary skill in the art that similar differences exist between perfluoroolefins and perfluoroalkylethylenes and therefore the Office's assertion that a process using a perfluoroalkylethylene may render obvious a process using a perfluoroolefin is not supportable.

Applicants submit that because those of ordinary skill in the art may not believe that a perfluoroolefin and perfluoroalkylethylene will react with an alcohol in the same way, the claimed invention is not obvious.

Applicants further submit that the obviousness rejection is not commensurate in scope with the prior art applied. For example, the Knaup reference is drawn to the reaction of perfluoroalkylethylene but the claimed invention is drawn to perfluoroolefins. Further, the processes to yield different products than those products obtained from the claimed process. Therefore, the solution to the problem of Satokawa is not found in Knaup because Knaup deals with a different chemical reaction.

It appears that the Office applies Knaup on the basis that Knaup discloses carrying out a reaction between a fluorinated unsaturated compound and an alcohol and, because the claimed process includes the reaction of a fluorinated unsaturated compound and an alkanol compound. However, Applicants do not claim the reaction of a fluorinated unsaturated compound with an alkanol. Instead, Applicants claim the reaction of a perfluoroolefin with an alkanol.

It appears that the Office expands the Knaup disclosure of a perfluoroalkylethylene to include the genus of all fluorinated unsaturated compounds. Applicants therefore respectfully submit that the Office's rejection is not commensurate in scope with the disclosure of the prior art and should therefore be withdrawn.

Applicants submit that the prior art process is disclosing perfluoroalkylethylene does not render obvious the claimed process wherein a perfluoroolefin is reacted with an alkanol. Applicants respectfully request the withdrawal of the rejections and the passage of all now-pending claims to Issue.

Respectfully submitted,

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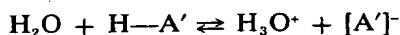
- (f) $\text{C}_6\text{H}_5\text{SO}_2\text{NH}_2$; (g) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{SH}$; (h) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$;
 (i) $\text{CH}_3\text{CH}_2\text{COOH}$; (j) $(\text{CH}_3)_3\text{COH}$; (k) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$;
 (l) $\text{CH}_3(\text{CH}_2)_4\text{COOH}$; (m) $(\text{COOH})_2$; (n) $(\text{CH}_3)_3\text{COOH}$; (o) $\text{C}_6\text{H}_5\text{OH}$;
 (p) $\text{CH}_3(\text{CH}_2)_4\text{CONH}_2$; (q) $\text{CH}_3\text{C}\equiv\text{CH}$; (r) $\text{CH}_3\text{CH}_2\text{NH}_2$.

§5.11 CORRELATION OF ACIDITY AND STRUCTURE—INDUCTIVE EFFECTS

The relative acidities of two acids H—A and H—A' in aqueous solution depend on the relative positions of the two equilibria:

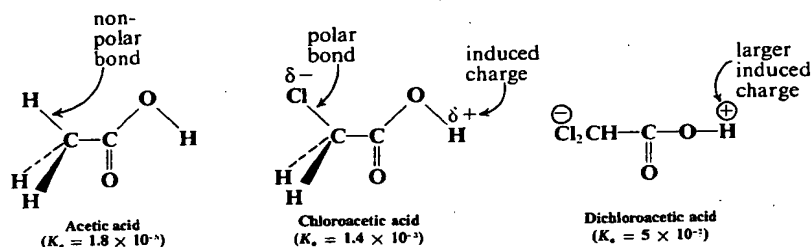


and



These equilibrium positions depend, in turn, on the relative thermodynamic stabilities of H—A vs. H—A' and of A^- vs. $[\text{A'}]^-$. Changing the structure of an acid from H—A to H—A' will cause a change in the stabilities of both the undissociated acid and the corresponding anion. If the effect of this structural change on these relative stabilities were known the acidity of H—A' relative to that of H—A could be predicted. Unfortunately, such data are not available, and the correlation of acidity changes with structural changes must be a more or less empirical one. Generally, we will find that an increase in acidity can be expected: (a) when the change from H—A to H—A' causes an increase in the positive character of the hydrogen atom which is to be released as a proton, and (b) when the change from H—A to H—A' leads to an increase in the resonance stabilization of the anion $[\text{A'}]^-$ relative to that of the anion $[\text{A}]^-$.

A common structural change that leads to an increase in acidity may be illustrated by considering the effect caused by substitution of a chlorine atom for one of the hydrogen atoms of the methyl group in acetic acid. The change from $\text{HCH}_2\text{CO}_2\text{H}$ (H—A) to $\text{ClCH}_2\text{CO}_2\text{H}$ (H—A') results in about a 100-fold increase in acidity. This may be explained by the fact that the H—C bond has a very small dipole, whereas the Cl—C bond has a large dipole, with its negative end pointed toward chlorine and its positive end toward carbon. The change from H—C to Cl—C therefore results in a large increase in the size of the positive charge on the carbon atom to which the chlorine is attached. This charge is relayed by induction (§4.3) to the next carbon atom, then to the oxygen atom, and finally to the hydrogen atom attached to oxygen. The net result is to induce a greater positive charge on the acidic hydrogen atom in chloroacetic acid than is present in acetic acid itself. Speaking in a general way we can say that the **inductive effect** of the chlorine atom has caused an increase in acidity of chloroacetic acid relative to acetic acid.



It must be kept in mind that the value of an acidity constant is determined by the position of an *equilibrium*. A more careful evaluation therefore calls for a comparison of the effect of substitution of Cl for H of acetic acid on both the relative ease of dissociation of the two acids *and* on the relative ease with which the two undissociated acids are formed in the reverse reactions. Since the structural change from $\text{HCH}_2\text{CO}_2\text{H}$ to $\text{ClCH}_2\text{CO}_2\text{H}$ results in a larger positive charge being induced on the hydrogen atom of the O—H group, this hydrogen atom becomes more susceptible to removal as a proton. Dissociation of chloroacetic acid is thereby favored relative to dissociation of acetic acid. In the corresponding anions the inductive effect of the chlorine atom will reduce the negative charge on the oxygen atoms of chloroacetate ion, $\text{ClCH}_2\text{CO}_2^-$, relative to that on acetate ion, $\text{HCH}_2\text{CO}_2^-$. As a result, chloroacetate ions will have less tendency to abstract a proton from H_3O^+ in the reverse reaction than will acetate ions. *The inductive effect of chlorine therefore operates in both the undissociated acid and in the anion to cause an increase in acidity.*

As would be anticipated, the chlorine atom is less effective in increasing acidity when it is introduced at a site farther removed from the acidic hydrogen atom. For this reason 3-chloropropionic acid, $\text{ClCH}_2\text{CH}_2\text{CO}_2\text{H}$ ($K_a = 1.0 \times 10^{-4}$) is less acidic than chloroacetic acid; it is, however, more acidic than acetic acid itself. Conversely, the ability of chlorine to enhance acidity becomes greater as it is brought closer to an acidic hydrogen atom. As a consequence, substitution of one of the hydrogen atoms of water by a chlorine atom leads to an approximately million-fold increase in acidity (K_a for ClOH is 5×10^{-8}), much of which can be attributed to an inductive effect.

Many groups are, like chlorine, electron-withdrawing with respect to hydrogen. In fact, all common groups with the exception of alkyl groups fall in this category. This means that most groups when substituted for a hydrogen atom of acetic acid will cause an increase in acidity. The relative acidities of acetic acids of the type YCH_2COOH are useful as a guide for determining the relative size of the inductive effects of various Y groups. Table 5-6 presents pK_a data for a variety of acetic acids.

From Table 5-6 it will be noted that the nitro (NO_2) and trimethylammonio [$(\text{CH}_3)_3\text{N}^+$] groups are most effective as Y groups in increasing the

TABLE 5-6
 pK_a Values for Acetic Acids, YCH_2COOH in Water at 25°
 (most Y groups exert electron-withdrawing inductive effects)

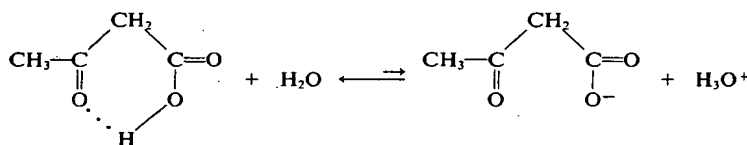
Y	pK_a^*	Y	pK_a^*	Y	pK_a^*
O ₂ N	1.68	Br	2.86	ClCH ₂	4.08
(CH ₃) ₃ N ⁺	1.83	F ₃ C	3.07	C ₆ H ₅	4.31
H ₃ N ⁺	2.31	I	3.12	CH ₂ =CH	4.35
CH ₃ SO ₂	2.36	CH ₃ O	3.53	Cl(CH ₂) ₂	4.52
N≡C	2.43	CH ₃ CO	3.58	Cl(CH ₂) ₃	4.70
F	2.66	CH ₃ S	3.72	H	4.76
HO ₂ C	2.80	HO	3.83	CH ₃	4.88
Cl	2.86	-O ₂ S	4.05		

* The conversion of pK_a values to K_a can be illustrated with chloroacetic acid; $pK_a = 2.86$; $-\log K_a = pK_a = 2.86$, so $\log K_a = -2.86$ or $\log K_a = -3 + 0.14$; the antilogarithm of -3 is 10^{-3} and that of 0.14 (see table of logarithms) is 1.38 (or 1.4 if two significant figures instead of three are used); therefore, $K_a = 1.4 \times 10^{-3}$.

acidity (decreasing pK_a) of acetic acid. Comparative effects of Y groups of interest are: $F > Cl, Br > I$; $CH_3O > CH_3S$; $Cl > ClCH_2 > ClCH_2CH_2 > ClCH_2CH_2CH_2$; $CH_3SO_2 > CH_3S$; $C_6H_5, CH_2=CH > H > CH_3$. Only alkyl groups (R, C_nH_{2n+1}) have negative inductive effects. We will make many references in future chapters to the electron-withdrawing properties of NO_2 , CN , CO_2H , CO_2Et , CH_3CO , CH_3SO_2 , CF_3 , and the like groups.¹⁰

¹⁰ The acidities of the YCH_2CO_2H acids listed in Table 5-6 in general give a good approximation of the relative size of the inductive effects of the Y groups. However, other factors *do* enter into the determination of these acidities and may sometimes dominate the inductive effects. For

example, it is known from other data that the inductive effect of the aceto group ($CH_3C(=O)-$) is considerably larger than that of the methoxyl group (CH_3O-). Yet the pK_a values for acetoacetic acid and methoxyacetic acid are nearly the same. The explanation is that hydrogen bridging in the undissociated acetoacetic acid molecule provides a stabilizing influence that is absent in its anion. The result is to shift the equilibrium for its dissociation to the left, thus partially offsetting the strong electron-withdrawing inductive effect of the aceto group. This acid-weakening effect is much smaller in methoxyacetic acid.



Hydrogen bridging in acetoacetic acid is acid weakening

Similar effects make a number of other groups appear to have smaller electron-withdrawing inductive effects than they really have. For example, the $-CO_2^-$ group appears to have an electron-releasing inductive effect, judging from the acidity constant of the hydrogen malonate ion, $HO_2CCH_2CO_2^-$ ($K_a = 2 \times 10^{-6}$). But other evidence (see, e.g., §20.1) suggests that the $-CO_2^-$ group, like the $-SO_3^-$ group, is actually electron-withdrawing. Strong hydrogen bridging in the hydrogen malonate ion inhibits dissociation of the proton.

KIRK-OTHMER

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TO
FUEL CELLS**



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FLUORINATED ALIPHATIC COMPOUNDS

The hydrogen atoms in alkanes can be partially or completely replaced by fluorine. Partially fluorinated alkanes are commonly called hydrofluorocarbons (HFCs) and the fully fluorinated derivatives are perfluorocarbons (PFCs). Alkanes whose hydrogens are replaced by both fluorine and chlorine are designated chlorofluorocarbons (CFCs), or hydrochlorofluorocarbons (HCFCs) if the replacement is incomplete. Similar designations are used for other halogenated fluorocarbons. Fluorinated aliphatics are further identified by a series of numbers related to the formula of the compound. In this numbering system for methane and ethane derivatives, the first digit on the right is the number of fluorine atoms in the compound, and the second digit from the right is one more than the number of hydrogen atoms. The third digit from the right is one less than the number of carbon atoms, but when this digit is zero, it is omitted. The remaining available positions in the compound are taken by chlorine atoms unless specified otherwise. For example, CCl_3F , CHClF_2 , CF_3CHF_2 , and CF_3CF_3 are designated CFC-11, HCFC-22, HFC-125, and PFC-116, respectively. When bromine is present, the same rules apply except that the letter B is used, followed by a number that indicates the number of chlorine atoms replaced by bromine. For example, CF_3Br and CHBrF_2 are coded BFC-13B1 and HBFC-22B1, respectively. In the fire extinguishing trade, the brominated derivatives are usually called Halons and have a different numbering system in which the digits from right to left are respectively the number of bromine, chlorine, fluorine, and carbon atoms. Any remaining available positions are hydrogen atoms. The above BFC and HBFC become H-1301 and H-1201 in this system. This numbering system has been extended systematically to both acyclic and cyclic compounds with more than two carbon atoms, but the code for distinguishing various isomers becomes rather complex (1).

Perfluorocarbons and Hydrofluorocarbons

Properties. Aliphatic PFCs have an unusual combination of physical properties relative to their hydrocarbon counterparts (2-5). The volatilities of PFCs are much higher than expected based on their molecular weights. For example,

tetrafluoromethane, mol wt 88, boils at -128°C , whereas *n*-hexane, mol wt 86, boils at $+69^{\circ}\text{C}$. Perfluorocarbons containing up to four carbon atoms boil somewhat higher than the corresponding hydrocarbons; the reverse is true of PFCs with more carbon atoms. Liquid PFCs are two to three times as dense as hydrocarbons with the same carbon skeleton, and aliphatic PFCs have among the lowest dielectric constants, refractive indexes, and surface tensions of any liquids at room temperature. The compressibilities and absolute viscosities of PFCs are considerably higher than those of hydrocarbons. Aliphatic PFCs are poor solvents for all materials except for those with low cohesive energies, such as gases and other PFCs. They are practically insoluble in water and only slightly soluble in hydrocarbons.

The extremely nonpolar character of PFCs and very low forces of attraction between PFC molecules account for their special properties. Perfluorocarbons boil only slightly higher than noble gases of similar molecular weight, and their solvent properties are much more like those of argon and krypton than hydrocarbons (2). The physical properties of some PFCs are listed in Table 1.

The physical properties of hydrofluorocarbons reflect their polar character, and possibly the importance of intermolecular hydrogen bonding (3). Hydrofluorocarbons often boil higher than either their PFC or hydrocarbon counterparts. For example, $1\text{-C}_6\text{H}_{13}\text{F}$ boils at 91.5°C compared with 58°C for $n\text{-C}_6\text{F}_{14}$ and 69°C for $n\text{-C}_6\text{H}_{14}$. Within the series of fluorinated methanes, the boiling point reaches a maximum for CH_2F_2 , which contains an equal number of hydrogen and fluorine atoms for maximum hydrogen bonding. The methane boiling points, however, also parallel their dipole moments, which reflect relative polar character: CH_3F ($\mu = 1.85\text{D}$), CH_2F_2 (1.97D), CHF_3 (1.65D), CF_4 (0.0D) ($1\text{D} = 3.336 \times 10^{-30} \text{ C}\cdot\text{m}$).

Hydrofluorocarbons invariably have higher refractive indexes, dielectric constants, and surface tensions, but lower densities than their PFC counterparts. The physical properties of some HFCs are listed in Table 2. Because of their very strong carbon-fluorine and carbon-carbon bonds (10), the chemical and thermal stability of PFCs is considerably higher in general than that of the corresponding hydrocarbons (3,11). Perfluorocarbons normally are significantly less reactive than hydrocarbons toward all chemical reagents except alkali metals. Molten alkali metals or alkali-metal hydrocarbon complexes degrade most fluorocarbons, and this reaction is used for their chemical analysis (3). Perfluorocarbons are not affected by acids or oxidizing agents and are not hydrolyzed below 500°C . Carbon tetrafluoride decomposes only slowly at carbon arc temperatures, and it does not react with Cu, Ni, W, or Mo at 900°C . Perfluorocarbons of higher molecular weight are less thermally stable, but temperatures approaching 1000°C are still required to decompose C_2F_6 or $n\text{-C}_3\text{F}_8$, and most PFCs are stable below 300°C . Partially fluorinated hydrocarbons are less stable and more reactive, especially when only one fluorine atom is present. Hydrogen fluoride can be eliminated by chemical or thermal action from hydrofluorocarbons.

Manufacture. The direct fluorination of hydrocarbons with elemental fluorine is extremely exothermic and difficult to control. Special methods including metal packing techniques, jet reactors, and high dilution have been developed to control the reaction, but currently they have limited industrial importance (12). Poly(carbon monofluoride), $(\text{CF})_x$, is one product that is made commercially by direct fluorination (of graphite) (13). The disadvantages of direct fluorination have

Table 1. Physical Properties of Aliphatic Perfluorocarbons (PFCs)^a

PFC number	Formula	CAS Registry Number	Molecular weight	Boiling point, °C	Melting point, °C	Liquid density, g/mL at °C	Liquid refractive index, n_D at °C	Critical temp, °C	Critical pressure, MPa ^b
14	CF ₄	[75-73-0]	88.01	-128.1	-183.6	1.613 ₋₁₃₀	1.151 ₋₇₃	-45.6	3.74
116	CF ₃ CF ₃	[76-16-4]	138.02	-78.2	-100.6	1.600 ₋₈₀	1.206 ₋₇₃	19.7	2.99
218	CF ₃ CF ₂ CF ₃	[76-19-7]	188.03	-36.7	-183	1.350 ₂₀		71.9	2.68
31-10	CF ₃ (CF ₂) ₂ CF ₃	[355-25-9]	238.04	-2.2	-128	1.543 ₂₀		113.2	2.32
C-318	cyclo-C ₄ F ₆	[115-25-3]	200.04	-5.9	-41.4	1.500 ₂₅	1.217 ₂₅	115.2	2.78
41-12	CF ₃ (CF ₂) ₃ CF ₃	[678-26-2]	288.05	29.2	-126	1.620 ₂₀	1.242 ₁₅	149	2.04
51-14	CF ₃ (CF ₂) ₄ CF ₃	[355-42-0]	338.07	58	-86	1.680 ₂₅	1.251 ₂₂	174.5	1.90
61-16	CF ₃ (CF ₂) ₅ CF ₃	[335-57-9]	388.08	82.5	-51	1.733 ₂₀	1.262 ₂₀	201.6	1.62
PP3 ^c	cyclo-C ₆ F ₁₀ (CF ₃) ₂ ^d	[335-27-3]	400.09	102	-70	1.828 ₂₅	1.290 ₂₅	241.5	1.88
PP6 ^e	cyclo-C ₁₀ F ₁₆ ^e	[306-94-5]	462.11	142	/	1.917 ₂₅	1.313 ₂₅	292.0	1.75
PP9 ^e	cyclo-C ₁₃ F ₁₇ (CF ₃) ^e	[306-92-3]	512.12	160	-70	1.972 ₂₅	1.320 ₂₅	313.4	1.66
PP11 ^f	cyclo-C ₁₄ F ₂₄ ^h	[306-91-2]	624.15	215	-20	2.03 ₂₅	1.335 ₂₅	377 ⁱ	1.46 ⁱ

^aRefs. 6-8.

^bTo convert MPa to psi, multiply by 145.

^cFlutec number (trademark of Rhône-Poulenc, Inc., RTZ Chemicals, ISC Division).

^dPerfluoro-1,3-dimethylcyclohexane.

^ePerfluorodecalin, *cis/trans* mixture.

^f-11.2 to 18.0°C, depending on *cis/trans* ratio.

^gPerfluoro-2-methyldecalin.

^hPerfluorotetradecahydrophenanthrene.

ⁱEstimated values.

Table 2. Physical Properties of Aliphatic Hydrofluorocarbons (HFCs)^a

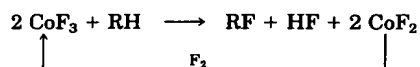
HFC number	Formula	CAS Registry Number	Molecular weight	Boiling point, °C	Melting point, °C	Liquid density, g/mL at °C	Liquid refractive index, n_D at °C	Critical temp, °C	Critical pressure, MPa ^b
23	CHF ₃	[75-46-7]	70.01	-82.2	-155.2	1.442 ₋₈₀	1.215 ₋₇₃	25.7	4.83
32	CH ₂ F ₂	[75-10-5]	52.02	-51.6	-136	1.200 ₋₅₀	1.190 ₂₀		
41	CH ₃ F	[593-53-3]	34.03	-78.3	-141.8	0.884 ₋₈₀	1.1727 ₂₀	44.6	5.86
125	CHF ₂ CF ₃	[354-33-6]	120.02	-48.5	-103	1.53 _{-48.5}	1.5012 ₁₉	72.4	3.52
134	CHF ₂ CHF ₂	[359-35-3]	102.03	-19.7	-89		1.250 ₂₀		
134a	CH ₂ FCF ₃	[811-97-2]	102.03	-26.5	-101	1.21 ₂₅		101.1	4.14
143	CHF ₂ CH ₂ F	[430-66-0]	84.04	5.0	-84			71.2	
143a	CH ₃ CF ₃	[420-46-2]	84.04	-47.4	-111.3	1.176 ₋₅₀	1.22 ₂₅	73.1	3.76
152	CH ₂ FCH ₂ F	[624-72-6]	66.05	30.7		0.913 ₁₉	1.28 ₂₅	107.5	
152a	CH ₃ CHF ₂	[75-37-6]	66.05	-25.8	-117	1.023 ₋₃₀	1.3011 ₋₇₂	113.5	4.50
161	CH ₃ CH ₂ F	[353-36-6]	48.06	-37.4	-143.2	0.818 ₋₃₇	1.3033 ₋₃₇	102.2	4.72
227ea	CF ₃ CFHCF ₃ ^c	[431-89-0]	170.03	-18	-129.5	1.407 ₂₅		101.7	2.91
245ca	CHF ₂ CF ₂ CH ₂ F	[679-86-7]	134.05	26	-82		1.30 ₁₅		
245cb	CF ₃ CF ₂ CH ₃	[1814-88-6]	134.05	-18				106.9	
254fb	CH ₂ FCH ₂ CF ₃	[460-36-6]	116.06	29.4		1.2584 ₂₅	1.2765 ₂₅		
272ca	CH ₃ CF ₂ CH ₃	[420-45-1]	80.08	-0.4	-104.8	0.9205 ₂₀	1.2904 ₂₀		
272fa	CH ₂ FCH ₂ CH ₂ F	[462-39-5]	80.08	41.6		1.0057 ₂₅	1.3190 ₂₆		
281ea	CH ₃ CHFCH ₃	[420-26-8]	62.09	-10	-133.4	0.7238 ₋₂₀	1.3075 ₋₁₀		
281fa	CH ₂ FCH ₂ CH ₃	[460-13-9]	62.09	-2.5	-159	0.7956 ₂₀	1.3115 ₂₀		

^aRefs. 5, 7-9.

^bTo convert MPa to psi, multiply by 145.

^cUnpublished data, Great Lakes Chemical Co.

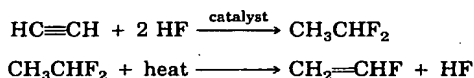
been overcome by the use of fluorine carriers, in particular, high valence metal fluorides such as cobalt trifluoride, CoF_3 , or potassium tetrafluorocobaltate, KCoF_4 . These reagents replace hydrogen and halogen atoms by fluorine and add fluorine to double bonds and aromatic systems (12).



Cobalt trifluoride is generated *in situ* by passing fluorine over cobalt difluoride contained in a horizontal, mechanically agitated steel reactor. The compound to be fluorinated is passed through the reactor at 150–300°C as a vapor in a stream of nitrogen. After the reaction is completed, the CoF_3 is regenerated by adding fluorine. Advances in process control technology have allowed the process to be run continuously by simultaneously introducing the fluorine and hydrocarbon into the cobalt fluoride bed (6). Principally, cyclic and higher molecular weight acyclic fluorocarbons are prepared by this method.

Fluorocarbons are made commercially also by the electrolysis of hydrocarbons in anhydrous hydrogen fluoride (Simons process) (14). Nickel anodes and nickel or steel cathodes are used. Special porous anodes improve the yields. This method is limited to starting materials that are appreciably soluble in hydrogen fluoride, and is most useful for manufacturing perfluoroalkyl carboxylic and sulfonic acids, and tertiary amines. For volatile materials with little solubility in hydrofluoric acid, a complementary method that uses porous carbon anodes and $\text{HF} \cdot 2\text{KF}$ electrolyte (Phillips process) is useful (14).

Hydrofluorocarbons are also prepared from acetylene or olefins and hydrogen fluoride (3), or from chlorocarbons and anhydrous hydrogen fluoride in the presence of various catalysts (3,15). A commercial synthesis of 1,1-difluoroethane, a CFC alternative and an intermediate to vinyl fluoride, is conducted in the vapor phase over an aluminum fluoride catalyst.



Perfluorocyclobutane is prepared by the thermal cyclodimerization of tetrafluoroethylene [116-14-3].

Health and Safety Factors. Completely fluorinated alkanes are essentially nontoxic (16). Rats exposed for four hours to 80% perfluorocyclobutane and 20% oxygen showed only slight effects on respiration, but no pathological changes in organs. However, some fluorochemicals, especially functionalized derivatives and fluoroolefins, can be lethal. Monofluoroacetic acid and perfluoroisobutylene [382-21-8] are notoriously toxic (16).

Uses. The chemical inertness, thermal stability, low toxicity, and nonflammability of PFCs coupled with their unusual physical properties suggest many useful applications. However, the high cost of raw materials and manufacture has limited commercial production to a few, small-volume products. Carbon

KIRK-OTHMER

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VOLUME 11

FLAVOR CHARACTERIZATION
TO
FUEL CELLS



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FLUOROETHANOLS

Ethanol may be readily fluorinated at C-2. Replacement of H by F at C-1 would lead to unstable compounds which readily form carbonyls by loss of HF.

Monofluoro Derivative

2-Fluoroethanol [371-62-0] (ethylene fluorohydrin, β -fluoroethyl alcohol), $\text{FCH}_2\text{CH}_2\text{OH}$, is a colorless liquid with an alcohol-like odor; mp, -26.45°C ; bp, 103.55°C ; d_4 , 1.1297; n_D^{18} , 1.13647; heat of combustion, -1214.0 kJ/mol (-290.16 kcal/mol) (1,2). It is miscible with water, stable to distillation, and low in flammability. It is the least acidic of the fluoroethanols, although more acidic than ordinary alcohols with a $\text{p}K_a$ value of 14.42 ± 0.04 in aqueous solution (3). Its most notable difference from the other fluoroethanols is its extreme toxicity (4-12). In mice an LD_{50} of 10 mg/kg has been measured (10-12). The toxicity is due to its facile oxidation in animals to derivatives of fluoroacetic acid [144-49-0], a known inhibitor of the tricarboxylic acid cycle of respiration. No effective antidote to this poisoning is known, although ethanol appears to diminish the lethal effects of 2-fluoroethanol in rats and monkeys (9).

In its chemical reactions, 2-fluoroethanol behaves like a typical alcohol. Oxidation (12) yields fluoroacetaldehyde [1544-46-3] or fluoroacetic acid; reaction with phosphorus tribromide (12) gives 1-bromo-2-fluoroethane [762-49-2]; addition to olefins results in ethers (13); and additions to isocyanates give carbamates (14). The alcohol can be prepared in 50% yield by the reaction of potassium fluoride with 2-chloroethanol at 175°C in high boiling glycol solvents (15). Alternatively, the addition of hydrogen fluoride to ethylene oxide (16) or the fluorination of 2-bromoethyl or 2-chloroethyl acetate with silver, potassium, or mercuric fluoride followed by hydrolysis gives the alcohol (1,2). 2-Fluoroethanol is not currently produced in commercial quantities, although (in 1992) it was available in research quantities for ca \$3/g.

Because of its high toxicity, special procedures should be followed by users of 2-fluoroethanol. Suggested precautions include working with it in sealed reactors at subatmospheric pressure and careful monitoring to ensure that contamination of the surroundings is minimized (17). Another potential hazard is the formation of the alcohol as a minor by-product in reactions such as those involving

boron trifluoride and ethylene oxide (18). Despite these problems, several potential uses for the alcohol and its derivatives have been reported. The alcohol has been used to control rodent populations (19) and, when labeled with ^{18}F , as a radiodiagnostic agent (20). Various derivatives have shown promise as herbicides or as agents to control mites and other plant pests (14,21–24).

Difluoro Derivative

2,2-Difluoroethanol [359-13-7], $\text{F}_2\text{CHCH}_2\text{OH}$, is a colorless liquid with an alcohol-like odor; mp, 28.2°C ; bp, 96°C ; d_4^{17} , 1.3084; n_D^{17} , 1.3320; heat of combustion, -1026 kJ/mol (-245.3 kcal/mol). It is stable to distillation and miscible with water and many organic solvents. As expected, its acidity lies between that of 2-fluoroethanol and 2,2,2-trifluoroethanol both in the gas phase (25) and in 50% aqueous ethanol solution (26), where its K_a of 1.0×10^{-12} is about 4.8 times smaller than that of trifluoroethanol.

2,2-Difluoroethanol is prepared by the mercuric oxide catalyzed hydrolysis of 2-bromo-1,1-difluoroethane with carboxylic acid esters and alkali metal hydroxides in water (27). Its chemical reactions are similar to those of most alcohols. It can be oxidized to difluoroacetic acid [381-73-7] (28); it forms alkoxides with alkali and alkaline-earth metals (29); with alkoxides of other alcohols it forms mixed ethers such as 2,2-difluoroethyl methyl ether [461-57-4], bp 47°C , or 2,2-difluoroethyl ethyl ether [82907-09-3], bp 66°C (29). 2,2-Difluoroethyl difluoromethyl ether [32778-16-8], made from the alcohol and chlorodifluoromethane in aqueous base, has been investigated as an inhalation anesthetic (30,31) as have several ethers made by addition of the alcohol to various fluoroalkenes (32,33). Methacrylate esters of the alcohol are useful as a sheathing material for polymers in optical applications (34). The alcohol has also been reported to be useful as a working fluid in heat pumps (35). The alcohol is available in research quantities for ca \$6/g (1992).

Trifluoroethanol

2,2,2-Trifluoroethanol [75-89-8], $\text{CF}_3\text{CH}_2\text{OH}$, is a colorless liquid with an ethanol-like odor; mp, -45°C ; bp, 73.6°C ; d_4^{25} , 1.3823; n_D^{20} , 1.2907; flash point (open cup), 41°C ; flash point (closed cup), 33°C ; no fire point (36); heat of combustion, -886.6 kJ/mol (-211.9 kcal/mol) (36); and dielectric constant (25°C), 26.14 (37). Many other physical and thermodynamic properties of the alcohol and its solutions have been published (36,38–41). It is the most acidic fluoroethanol with an ionization constant of 4.3×10^{-13} (42). It is stable to distillation and miscible with water and many organic solvents. It has the unusual property of dissolving most polyamides, both nylons (43) and polypeptides (44), at room temperature. Because of its excellent combination of physical and thermodynamic properties, 2,2,2-trifluoroethanol–water mixtures (also known as fluorinols) have application as working fluids in Rankine-cycle engines for recovering energy from waste heat sources (36,45,46). Its high ionizing power and low specific conductance make the alcohol

useful as a solvent for ionic reactions and conductometric titrations (47), and basic research into solvolysis mechanisms (48–50).

Chemically, 2,2,2-trifluoroethanol behaves as a typical alcohol. It can be converted to trifluoroacetaldehyde [75-90-1] or trifluoroacetic acid [76-05-1] by various oxidizing agents such as aqueous chlorine solutions (51) or oxygen in the presence of a vanadium pentoxide catalyst (52). Under basic conditions, it adds to tetrafluoroethylene and acetylene to give, respectively, 1,1,2,2-tetrafluoroethyl 2',2',2'-trifluoroethyl ether [406-78-0] (53) and 2,2,2-trifluoroethyl vinyl ether [406-90-6] which was used as the inhalation anesthetic Fluroxene. Its alkoxides react with bromoethane to give trifluoroethyl ethyl ether [461-24-5], bp 50.3°C. Similarly prepared is bis(trifluoroethyl) ether used as the convulsant drug Fluorothyl as a substitute for electric shock therapy. As the trichlorosulfonate ester, trifluoroethanol is used to introduce the trifluoroethyl group into the anxiolytic drug Halazepam [23092-17-3] (54). 2,2,2-Trifluoroethanol is also the starting material for the anesthetic Isoflurane (1-chloro-2,2,2-trifluoroethyl difluoromethyl ether [26675-46-7]) (55,56) and Desflurane (2-difluoromethoxy-1,1,1,2-tetrafluoroethane [57041-67-5]) (57).

Trifluoroethanol was first prepared by the catalytic reduction of trifluoroacetic anhydride [407-25-0] (58). Other methods include the catalytic hydrogenation of trifluoroacetamide [354-38-1] (59), the lithium aluminum hydride reduction of trifluoroacetyl chloride [354-32-5] (60) or of trifluoroacetic acid or its esters (61,62), and the acetolysis of 2-chloro-1,1,1-trifluoroethane [75-88-7] followed by hydrolysis (60). More recently, the hydrogenation of 2,2,2-trifluoroethyl trifluoroacetate [407-38-5] over a copper(II) oxide catalyst has been reported to give the alcohol in 95% yield (63).

The largest producer of trifluoroethanol is Halocarbon Products Corp. Other producers include Japan Halon and Rhône-Poulenc. Commercial quantities sell for approximately \$20/kg (1992).

Toxicity studies on trifluoroethanol show acute oral LD₅₀, 240 mg/kg; acute dermal LD₅₀, 1680 mg/kg; and acute inhalation L(ct)₅₀, 4600 ppm·h. Long-term subchronic inhalation exposure to 50–150 ppm of the alcohol has caused testicular depression in male rats, but no effects were noted at the 10 ppm level (32). Although the significance of the latter observations for human safety is unknown, it is recommended that continuous exposure to greater than 5 ppm or skin contact with it be avoided.

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